



Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
--------------------	-------------	-----------------------	------------------

11/27/95 06/07/95 MEHLHORN

R 028723-063

EXAMINER

021833 HM12/1116
BURNS DOANE SWECKER & MATHIS L L P
POST OFFICE BOX 1404
ALEXANDRIA VA 22313-1404

ART UNIT	PAPER NUMBER
----------	--------------

1615

25

DATE MAILED: 11/16/00

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

- ☒ Responsive to communication(s) filed on 9-11-00
- ☒ This action is **FINAL**.
- ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire -3- month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

- ☒ Claim(s) 46-65 is/are pending in the application.
- Of the above, claim(s) _____ is/are withdrawn from consideration.
- ☐ Claim(s) _____ is/are allowed.
- ☒ Claim(s) 46-65 is/are rejected.
- ☐ Claim(s) _____ is/are objected to.
- ☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

- ☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
- ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
- ☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
- ☐ The specification is objected to by the Examiner.
- ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
- ☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been
- ☐ received.
- ☐ received in Application No. (Series Code/Serial Number) _____
- ☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

- ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

- ☐ Notice of Reference Cited, PTO-892
- ☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
- ☐ Interview Summary, PTO-413
- ☐ Notice of Draftsperson's Patent Drawing Review, PTO-948
- ☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

Art Unit: :1615

DETAILED ACTION

The request for the extension of time and amendment filed on 9-11-00 and the letter regarding the fee filed on 10-17-00 are acknowledged.

Claims included in the prosecution are 46-65.

Claim Rejections - 35 U.S.C. § 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. Claims 46-54, 56-57, and 61-64 are rejected under 35 U.S.C. 102(b) as being anticipated by Nichols (BBA, 1976).

Nichols discloses a method of preparation of liposomes using instant method (note entire publication, page 270 in particular). The drugs loaded include epinephrine (page 271). The method involves preparing liposomes with acidic pH and titrating them with a base to create a pH gradient and adding a basic drug such as epinephrine to load the drug.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that the present invention is based on the surprising discovery

Art Unit: :1615

that the use of pH gradients, in accordance with the invention, to load liposomes allows for the rapid uptake of drugs or chemical species by the liposomes and the chemical species loaded liposomes of the invention are stable in the presence of the pre-imposed pH gradient and in the absence of the pre-imposed pH gradient. Applicants further argue that in contrast to the present invention, Nichols et al teach the uptake of catecholamine by liposomes maintaining a pH gradient. Applicants' further arguments are based on the differences in the properties of the preparation. These arguments are not found to be persuasive since the differences argued are not reflected in the claims. The reference teaches the same steps as recited in the instant claims. Applicants' arguments with regard to 'stable liposomes' has already been addressed by the examiner in the previous action.

3. Claims 46-54, 57 and 61-64 are rejected under 35 U.S.C. 102(b) as being anticipated by Deamer (BBA, 1972) of record.

Deamer discloses a method of preparation of liposomes using instant method (note entire publication, page 270 in particular). The compounds loaded include are amines (note abstract and Method section). The method involves preparing liposomes with acidic pH and titrating them with a base to create a pH gradient and adding a basic amine.

Applicants' arguments have been fully considered, but are not found to be persuasive. Applicants' argue that like Nichols, Deamer teaches that the physical chemistry of pH gradients could be used to accumulate entrap a drug composition in liposomes. Applicants further argue that the primary focus of Deamer is to analyze the quenching

Art Unit: :1615

effect on the fluorescent probes in the presence or pH gradients. These arguments are not found to be persuasive for the following reasons. First of all, instant claims are method of preparation claims and the reference teaches the same method with the same steps, although the purpose for which the method is used is different. Secondly, instant claims recite the method of loading the chemical species and the compound loaded in Deamer's method is a chemical species.

4. Claims 46-54, 59 and 61-64 are rejected under 35 U.S.C. 102(b) as being anticipated by Cramer (BBRC, 1977) or Kano (BBA, 1978) already of record.

The references of Cramer and Kano disclose a method of loading substances using pH gradient (note the abstracts). The method involves the preparation of liposomes and lowering the pH of the external medium. The compounds loaded are acidic in nature (note the abstract and Materials and methods).

Applicants' arguments to these rejections have been considered, but are not found to be persuasive. Applicants' arguments for the rejections over these references are essentially similar to those for rejections over Nichols and Deamer and hence the same reasoning is applicable. In essence, it should be pointed out that the references teach the same method having the same steps although the goals are different.

Art Unit: :1615

Claim Rejections - 35 U.S.C. § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

6. Claims 46-65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nichols or Deamer or Cramer or Kano cited above.

Nichols and Deamer do not teach the establishment of the pH gradient by the addition of an acid. It is deemed however, to be within the skill of the art of chemistry that if the internal medium is basic one can only establish a gradient by the addition of a acidic substance (that is, altering the pH). Nichols does not teach instant drugs. However, Nichols and Deamer teach the concept of loading a chemical species into the liposomes using a pH gradient. It would have been obvious to one of ordinary skill in the art to load any drug with the expectation of similar loading since Nichols and Deamer teach the principle of loading.

Cramer and Kano do not teach the establishment of the pH gradient by the addition of a base. It is deemed however, to be within the skill of the art of chemistry that if the internal medium is acidic one can only establish a gradient by the addition of a basic substance (that is, altering the pH). Cramer and Kano do not teach instant drugs. However, Cramer and Kano teach the concept of loading a chemical species into the

Art Unit: :1615

liposomes using a pH gradient. It would have been obvious to one of ordinary skill in the art to load any drug with the expectation of similar loading since both references teach the principle of loading.

Applicants argue that even though liposomes with pH or electrical potentials across their membranes could accumulate drugs with pH-responsive groups within their molecular structures or drugs having hydrophobic ions as part of their molecular structure as taught by the references cited, the loaded liposomes of the invention are stable and do not release their drugs upon being diluted into large volumes of body fluids. This argument is not found to be persuasive since applicants' provide any comparative data to this effect.

Applicants argue that the experiments involving the injection of liposomes into rat demonstrate the feasibility of the liposome drug delivery system in vivo and prior to these experiments, one would not have known whether such drug entrapped liposomes would wreak havoc on the biogenic amines that play a vital role in animal physiology. These arguments would have been pertinent if the claims are method of use claims; however instant claims are method of preparation claims and hence are not applicable.

Furthermore, as pointed out above, instant claims do not recite any critical features which enable instant product to be different from prior art's product.

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

Art Unit: :1615

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to *G.S. Kishore* whose telephone number is (703) 308-2440.

The examiner can normally be reached on Monday-Thursday from 6:30 A.M. to 4:00 P.M. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, T.K. Page, can be reached on (703)308-2927. The fax phone number for this Group is (703)305-3592.

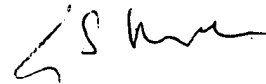
Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [thurman.page@uspto.gov].

**All Internet e-mail communications will be made of record in the application file.
PTO employees do not engage in Internet communications where there exists a possibility**

Art Unit: :1615

that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703)308-1235.



Gollamudi S. Kishore, Ph. D

Primary Examiner

Group 1600

gsk

November 15, 2000